Science Advisory Board (SAB)
Supplemental Guidance for Assessing Cancer Susceptibility (SGACS)
From Early Life Exposure to Carcinogens Review Panel
Public Meeting
May 12-14, 2003 – Sheraton Crystal City, Arlington, VA

Panel Members:	See Panel Roster (Attachment A)	
Dates and Times:	Monday, May 12, 2003, 1:00 to 5:00 p.m. EDT Tuesday, May 13, 2003, 8:30 a.m. to 5:15 p.m. EDT Wednesday, May 14, 2003, 8:30 a.m. to 4:45 p.m. EDT	
Location:	Sheraton Crystal City Hotel 1800 Jefferson Davis Highway Arlington, VA 22202	
Purpose:	The purpose of this public meeting was to continue the review of the EPA Office of Research and Development (ORD) draft document titled, "Supplemental Guidance for Assessing Cancer Susceptibility From Early-Life Exposure to Carcinogens" (SGACS).	
Attendees:	Chair:	Dr. Henry Anderson
	SAB Members:	Dr. James Klaunig Dr. Ulrike Luderer Dr. Anne Sweeney Dr. Richard Vetter
	CHPAC Members:	Dr. Daniel Goldstein Dr. Melanie Marty
	SAP Members:	Dr. Stuart Handwerger Dr. Steven Heeringa Dr. Christopher Portier
	EPA SAB Staff:	Dr. Suhair Shallal Dr. Vanessa Vu

Other Persons Attending: *(in order of their appearance on the Agenda)*

Dr. William Wood, Executive Director, U.S. EPA Risk Assessment Forum (RAF)
Dr. James Cogliano, World Health Organization, International Agency for Research on Cancer (WHO/IARC)
Dr. Hugh Barton, Experimental Toxicology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development (NHEERL/ORD)

Dr. David Hoel did not attend due to illness and was therefore not expected to participate in subsequent teleconferences to revise the draft report.

Other EPA personnel and members of the public, as noted on the sign-in sheets (Attachment B).

Meeting Summary

The meeting generally followed the schedule set out in the agenda. (Attachment C) The meeting adjourned at 5:15 p.m. on May 12, 3:45 p.m. on May 13, and 4:00 p.m. on May 14.

Opening Remarks / Panel Formation Process

Dr. Suhair Shallal, Designated Federal Officer (DFO) for SGACS, welcomed participants to the public meeting. She provided a brief overview of panel formation, which followed EPA's new process with a slight modification to take advantage of the unique expertise in children's risk assessment provided by members of the FIFRA Science Advisory Panel (SAP) and the Children's Health Protection Advisory Committee (CHPAC) as well as the SAB. Conflict of interest, perceived impartiality, expertise, and balance of the panel were considered in making the final decision. No conflict of interest or financial interests exist. Dr. Shallal noted that documents related to panel formation are available on the SAB web site.

Dr. Vanessa Vu, SAB Staff Office Director, welcomed participants to the meeting and noted that the partnership among the SAB, FIFRA SAP, and CHPAC would enable a credible scientific peer review of the SGACS document. She thanked the panel members, agency officials, and public commenters for their participation.

Introductory Remarks and Introduction of Panel Members

Dr. Henry Anderson, SGACS Chair, welcomed participants to the meeting. He expressed his appreciation to the panel members for providing their comments on the SGACS draft in advance of the meeting, reviewed briefly the schedule for the three days, and asked panel members to introduce themselves for the record.

Dr. Anderson invited Dr. Bill Farland (ORD) to speak. Dr. Farland extended his welcome and thanks to the panel. He noted that EPA's work on the Cancer Guidelines, which began in 1984, was a continuing process to identify and develop the best science in support of the Agency's decisions. The SGACS is a supplement to the Cancer Guidelines, prepared in response to a request by an earlier review panel. Dr. Farland then introduced the EPA speakers.

Agency Introductory Remarks

Dr. Bill Wood (RAF) reviewed the evolution of risk assessment at EPA, beginning in the 1970s. (Slides, Attachment D) Since 2000, he said, EPA has further refined existing tools; examined complex mixtures, susceptible populations and life stages; worked on harmonization of cancer and non-cancer guidance; and worked to develop an interface between risk assessment and cost-benefit analysis.

Dr. Wood also discussed the history of the Cancer Guidelines, issued in 1986, with revisions proposed in 1996. In its review, the SAB complemented EPA on the incorporation of new science and on moving away from default assumptions, but concluded that the revised Guidelines fell short regarding sensitive subpopulations and life stages. In 1999, the SAB reviewed EPA's revisions of major sections of the Guidelines, with a focus on children's cancer risk. In November 2001, EPA issued a notice of intent to finalize the Guidelines, invited additional public comment, highlighting the children's issue.

In its 1999 review, Dr. Woods said, the SAB noted that EPA had worked for many years to revise the Cancer Guidelines and recommended that the Agency move forward to finalize them. The SAB noted that while some outstanding issues required improvement- that should not delay the Guidelines' issuance. The SAB identified childhood susceptibility, or age-dependence in carcinogenesis, as an area requiring additional work, and recommended quantitative analysis of the literature on adult and perinatal carcinogenesis, calculation of risk estimates, and comparison of potency estimates.

Dr. Wood said that the SGACS will be issued as a supplement to the Cancer Guidelines when finalized. The Guidelines and SGACS are on parallel tracks, and the SGACS is a separate document so that it can be updated more frequently than a revision of the entire Guidelines can occur.

The goal of this meeting, Dr. Wood stated, is for the panel to review the soundness of the Agency's position that the analysis and underlying scientific information presented in the SGACS support the conclusion that there is greater susceptibility for the development of tumors as a result of early exposures to mutagenic chemicals. Dr. Wood then briefly reviewed the charge questions. (Attachment E)

Guidelines for Carcinogen Risk Assessment

Dr. Jim Cogliano, currently at WHO/IARC, was formerly at EPA and worked on both the Cancer Guidelines and the SGACS. (Slides, Attachment F) The intent of the SGACS, he said, is to provide the scientific support for the position that a life stage is not a separate part of the population, that is, childhood is a stage through which all adults go.

The general cancer risk assessment framework at EPA follows the National Academy of Sciences (NAS) paradigm, Dr. Cogliano said. Hazard assessment is summarized in a weight-of-evidence narrative. The conclusion also includes the conditions of carcinogenicity (route, magnitude, duration of exposure; susceptible populations and life stages), a summary of the key evidence, a summary of the key default assumptions, and a summary of the potential modes of action.

Mode of action (MOA) refers to the sequence of key events and processes that result in cancer formation. Understanding a chemical's MOA allows better understanding of the chemicals relevance to human cancer risk, Dr. Cogliano said. The relevance of a MOA is assessed by examining the similarities and differences between test animals and humans, and susceptibility is assessed by considering whether key events of the MOA can differentially affect a particular population or life stage.

Dr. Cogliano reviewed EPA's approach to dose-response assessment, which is summarized by a slope factor or reference dose (RfD). Because the doses in animal studies are typically much higher than human environmental doses, EPA must make a judgment regarding estimation of risk outside the range of the bioassays. The prediction of the shape of a dose-response curve depends on the chemical's MOA

The RfD is used for chemicals with MOAs that are nonlinear at low doses. The point of departure is a low risk level from an animal bioassay or epidemiologic study, not a level at which people should be exposed in the environment. Uncertainty factors are used to address differences between experimental systems and human environmental exposures. The RfD does not estimate a risk level, Dr. Cogliano said. It provides no explicit characterization of the dose-response curve below the point of departure and can be thought of as a degree of comfort that people are not at an increased cancer risk.

Dr. Cogliano then discussed exposure assessment, which is done for each population and exposure scenario. The lifetime average daily dose includes all the pathways of exposure, and can consider year-to-year differences. Exposures for years 1 to 70 are summed up and divided by 70 years (on the rationale that the animal studies involve lifetime dosing). This approach works well if exposures are assumed to be constant; however, occupational exposures occur only in adulthood and soil exposures from playing are likely to be higher in childhood.

For partial lifetime exposures, a short-term exposure is prorated over a full lifetime, Dr. Cogliano said. The approach does not account for when during the lifetime the exposure occurs; the same average dose is calculated if the exposure occurs in the first 5 years of life or beginning

at age 50. Any five-year exposure will give the same result. Dose-response and exposure assessments are put together to calculate an upper bound on risk, by multiplying the slope factor by the lifetime average daily dose.

Dr. Cogliano then reviewed EPA's new Cancer Guidelines. He noted that there is an emphasis on MOA throughout the guidelines. A weight-of-evidence narrative replaces the letter classification scheme. A two-step dose-response process separates modeling the observed data from extrapolation to lower doses. There is also an emphasis on analyzing all the data before invoking defaults. Differential risks to children are explicitly addressed, although there is no overall assumption that children are more or less susceptible than adults. The Cancer Guidelines are interested in both effects manifest during childhood and early-life exposures that can contribute to effects at any time later in life.

The SGACS emphasizes childhood exposures that contribute to risks later in life, because that is where the quantitative data are, Dr. Cogliano said. In the past, childhood exposures have generally been treated like any other partial lifetime exposure; a single slope factor is applied to all exposures. An exception is EPA's assessment of vinyl chloride, in which specific bioassays allowed the comparison of exposures starting at age 1 day and age 13 weeks; these studies showed a much higher risk when exposure occurred during the period of development, consistent with the existence of a window of susceptibility. For vinyl chloride, two exposure assessments are done, one using the early life window, and one the lifetime exposure.

Dr. Cogliano reviewed the framework of the draft SGACS. Like the Cancer Guidelines, the SGACS invokes a default if information is lacking, following the advice of the SAB in 1999 to be public health protective. When the Agency has an early-life bioassay, such as for vinyl chloride, it will use that assay, but for most chemicals, this critical information will be lacking. The SGACS concludes that biological susceptibility can vary during life. Decisions are based on MOA, which allows consideration of differences in biological susceptibility during childhood. The approach increases the estimated risk for childhood exposures to carcinogens that act through a mutagenic MOA. There is a modest increase (less than 2-fold) for exposures that are relatively constant throughout life, and up to a 10-fold increase for a short term exposure that occurs during infancy.

Dr. Vetter asked for further explanation of the adjustment factors. Dr. Cogliano said that exposure during the first two years of life is multiplied by 10-fold adjustment factor, which would represent a 10-fold increase in cancer risk. If exposure continues throughout life, the lifetime risk would be multiplied by a factor of less than 2.

Dr. Marty asked if it would be appropriate, when risk is incurred in the first two years of life, for risk to be multiplied by 2/70. Dr. Cogliano said that 2/70 is too severe a discounting factor for a short exposure that occurs during critical period. If after discounting, the risk were multiplied by 10, it would still be a small part of lifetime risk (20/70), but would not be discounted so much.

Dr. Heeringa asked how risk assessors interpreted the term "public-health protective" and whether it could be quantified. Dr. Cogliano said that risk assessment is the scientific assessment of risks, and upper bounds, with scientific judgment. Risk management refers to actions that are taken. The risk assessor wants to assure that risk is not under-represented, and the degree of protection being built in is unquantifiable. Risk assessors do what they can to not understate risks, while still giving a good picture of risk.

Dr. Anderson noted that EPA has chosen defaults of 10 or 3 for mutagens, but that for other agents, the default is 1. He asked about the rationale for that, commenting that anything greater than 1 could be viewed as public health protective. Dr. Cogliano said that for chemicals that cause cancer other than by mutagenicity, EPA thinks that linear extrapolation at low doses is already health protective, and for mutagenicity, EPA thinks that linear dose response is not reasonable. Since it does not add any protectiveness to the assessment, EPA thought some additional factor was warranted.

Public Comments

Engine Manufacturers Association – Dr. Resha Putzrath (for Dr. Gail Charnley)

Dr. Putzrath suggested that some issues in the draft SGACS required refinement, including the definition of relative potency, to show that it is the ratio of doses required to produce the same effect, not the ratio of responses to the same dose. Dr. Putzrath also called that the extrapolation from high to lower doses "tenuous." She said that the relative potency for children and adults is unlikely to be constant, and noted that sensitivity can change as the dose changes. Dr. Putzrath said that adjustments should be made on the maximum likelihood dose-response curve rather than on the upper bound, and suggested that there are insufficient data to quantify the age adjustment for mutagenic carcinogens. Dr. Putzrath described limitations of the studies cited in the SGACS, including single dose levels, poor reporting, incomparable treatment regimens, and unknown doses. Finally, Dr. Putzrath pointed out that there is an inherent assumption in the SGACS that mutation is the critical factor, while the rate-limiting step is likely to change with dose and is unlikely to be mutation.

American Chemistry Council (ACC) – Dr. Lorenz Rhomberg, Gradient

Dr. Rhomberg noted technical problems with measurements of relative susceptibility, and raised questions about the data analysis in the SGACS. He said that the assumption that the end-of-life response is the sum of separate tumors caused by early and late exposures is not in accord with the multistage understanding of carcinogenesis. Dr. Rhomberg recommended that the SGACS consider a hazard function, rather than overall tumor susceptibility. He proposed that the SGACS contains overly simplistic adding and subtracting of risks, improper combination of independent risks, and inconsistent definitions of juvenile and adult. The studies cited use doses that are not equivalent in juvenile and adult exposures, and have problems with the length of follow-up (variation among dose groups, no accounting for early deaths, bias due to longer

follow-up of early life exposures, and decreasing follow-up of chronic exposures). Dr. Rhomberg recommended that EPA use the hazard function to look at the development of risk over time.

American Chemistry Council (ACC) – Dr. Leslie Hushka, Exxon Mobil

Dr. Hushka suggested that the defaults were policy choices lacking scientific justification. Dr. Hushka proposed that the SGACS contained contradictions regarding the use of a MOA determined in adults in children and conflicting approaches to extrapolation. In his opinion, imposing a default for early-life exposures is inconsistent with accepted scientific principles and practices. He called for EPA to establish that children are no more sensitive than adults; to assume that MOAs that operate in adults operate in children; and to assess specific data to determine if they apply. Decisions on the adequate protection of children are distinct from assessing their potential sensitivity, and the current methodology is sufficiently public health protective, Dr. Hushka said.

American Chemistry Council (ACC) – Dr. Terry Quill, Duane Morris

Dr. Quill said that EPA's current assessment methodology provides adequate protection. He noted that EPA proposes to impose new conservative default assumptions, while still applying all the defaults detailed in the Cancer Guidelines. He suggested that early-life exposures may increase, decrease, or have no effect on susceptibility, and said that the SGACS does not support a generalization of increased risk. Regarding the necessity for additional defaults, Dr. Quill said that, using the available science, EPA did not demonstrate that early-life exposures typically lead to increased cancer. He called on EPA to avoid overly conservative risk assessments because this deprives risk managers of policy options, deprives risk communicators of best estimates of risk, can have unnecessary adverse economic and other societal impacts; and can result in misallocation of limited resources. Conservative assumptions and defaults are already part of EPA's cancer risk assessment methodology, and are health protective. The available science does not support sweeping new defaults to account for early life exposure. Dr. Quill proposed that the existing methodology is sufficiently protective, the SGACS should be withdrawn, and EPA should reexamine the question of low-dose susceptibility, beginning by establishing a research program.

American Chemistry Council (ACC) – Dr. Richard Becker

Dr. Becker said that it is premature to establish policy based on such limited data. To get the necessary data, he recommended that EPA establish a research program. This includes defining the question/hypothesis; using experiments designed for different purposes to examine comparative risks of different exposures; and designing the experiments appropriately. The types of analyses to consider include time-to-tumor analyses (which give important information); extrapolating to humans (including asking what developmental stages are being evaluated); *in utero* and transplacental studies (which may or may not result in a greater response); relating

animal models of transplacental exposure to developmental landmarks in humans (e.g., late development of p450 enzymes in humans). In conclusion, Dr. Becker said that EPA needs to undertake a more thorough analysis along the lines of the ACC's suggestions, and that it is premature to implement the Draft SGACS.

FQPA Implementation Working Group – Mr. Ed Gray

Mr. Gray pointed out that the SGACS is not required by or related to the FQPA and that it will not be used to produce lower RfDs or exposure levels for children. The SGACS addresses the underestimation of the cancer rate in adults due to the use of studies in which animals are dosed after they mature, and it is not unreasonable to revise risk assessments to account for early life exposures, he said. Mr. Gray said that the SGACS document contains incorrect and misleading descriptions of the studies used. He also raised questions regarding the 11 studies used to derive the additional safety factor, namely that eight of the studies were done by one author using one strain of mouse; all use liver tumors as the endpoint; eight use either benzene or safrole; there appear to be sex differences; and the data are not new (the most recent is 1983). Mr. Gray also questioned the logic of EPA's proposed break point of two years, suggesting that six months might be more appropriate.

CropLife America – Dr. James Lamb, BBL Sciences

Dr. Lamb addressed the use of studies of atomic bomb survivors in the SGACS document. He noted that there is some useful information in the studies, but as EPA noted, there are also recognized differences between radiation and mutagenic chemicals. He said that while relative risks for adults and children exposed to large doses of ionizing radiation are similar, the absolute risks are not, and age at exposure does not appear as significant as does latency. He noted that due to low background rates, fewer cancers are required to double the absolute risk in children compared to adults. Dr. Lamb said that there are explanations other than higher sensitivity for the increases noted in the studies of children. The data did not universally support increased susceptibility in children, e.g., risks for some rapidly growing tissues were increased while others were not. Dr. Lamb also called for clear and consistent definitions of terms used in the document and a better description of how things will be weighed; said that a stronger scientific basis was needed for some of the proposed adjustments and that the SGACS document appeared to be driven by a lack of evidence rather than by the existence of evidence.

CropLife America – Dr. Jim Stevens, Wake Forest University

Regarding the data on non-mutagenic agents, Dr. Stevens suggested that EPA should establish criteria for the use of rodent bioassay data to estimate juvenile cancer susceptibility. He noted that EPA had made several critical assumptions regarding these studies. He opined that three of the six studies in the table were sub-standard and/or provided insufficient detail to be used. While the Chhabra studies were adequate, Dr. Stevens said that comparable juvenile and adult doses were unlikely in those studies. He also commented that a susceptibility ratio should not be

calculated when the tumor incidence is not statistically different from controls for each subgroup.

CropLife America – Dr. Robert Sielken, Syngenta and CropLife America

In the context of age-dependent dosing (that is, dosing that is not continuous throughout the lifetime), Dr. Sielken asked if the models that EPA suggested be used were the correct measures mathematically. The ratio of risk to exposure duration is not independent of the duration of the experiment, he said, and so is not a valid measure for comparing different age-dependent exposures. Using an example in which the first of two stages was dose-dependent, he said that there will be different outcomes under different scenarios, and that arbitrary factors will not work for all chemicals or all MOAs. Dr. Sielken presented a second example, in which the second of the two stages was dose-dependent, and noted that this could give the opposite result, namely, that adult exposure increases the tumor probability more than juvenile exposure does. Dr. Sielken suggested that time-to-tumor data would be useful for addressing the topic.

Toxicology Excellence for Risk Assessment – Dr. Lynne Haber

Dr. Haber urged EPA to address the toxicokinetic and toxicodynamic differences between children and adults in greater detail. She noted that clearance is lower at birth than in adults, but is greater for ages 6 months to two years than in adults. Because metabolic differences can be either detoxification or activation, children can be either more or less sensitive. Dr. Haber noted that EPA's recommendation for bioassays to begin immediately after the animals are weaned corresponds to the period of 1 year to adolescence in humans. She suggested that EPA acquire data to investigate quantitatively why children are more sensitive. Dr. Haber called for EPA to be clear about how to use data to move away from the defaults. She also noted that the available studies were not designed for direct comparison; encouraged stakeholders to cosponsor animal studies with EPA; and proposed that EPA re-do the analysis in the SGACS using the ED_{10} approach.

Natural Resources Defense Council (and co-signers) – Dr. Jennifer Sass

Dr. Sass recommended that EPA add language clarifying that health-protective assumptions must always be used as the default. She urged the panel to recommend that non-mutagenic carcinogens be treated in the same way as mutagenic carcinogens. She also urged them to recommend that the definition of susceptible life stages extend from fetal development to age 2, age 2-6, and then age 7-17, to encompass puberty. She suggested that the panel recommend that endocrine disruptors be added as a class of chemicals to which children are particularly susceptible, and that prenatal exposure be recognized as a period of developmental sensitivity. Regarding MOA, Dr. Sass recommended adding a paragraph that addresses not only the adequacy of the evidence, but certainty for protecting public health. She also recommended an analysis of model uncertainty be included in all cases when a model is used to extrapolate to lower doses.

Physicians for Social Responsibility – Susan Marmages

Ms. Marmages suggested that there were five areas of deficiencies in the draft SGACS, the first of which was the failure to consider prenatal exposures. The second area was the failure to address acute exposures in children; the current model averages over life stages, and acute exposures during short windows need to be considered. She also suggested that the document has an inappropriate focus on mutagenic MOA. Ms. Marmages said that she was concerned that the age 2-15 life stage is too broad; she suggested it should be broken down, and that there be a differentiation between males and females in the pubertal period. She said her organization strongly supports the use of additional safety factors to address increased susceptibility, and expressed concern that the largest factor used in the document represents a median of ratios. Ms. Marmages suggested that the adjustment factors be "fine-tuned" to more age categories, but if not, that a factor of 10 be used for all children, and a factor of 10 or more be used for the prenatal period.

Dr. Anderson thanked the speakers and the audience. The first day of the meeting adjourned at 5:15 p.m.

Tuesday, May 13, 2003

Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens

Dr. Hugh Barton (NHEERL/ORD) noted that the SGACS document only addresses early life exposure and cancer at a later stage in life, not childhood cancer *per se*. (Slides, Attachment G) EPA's current approach treats every period of exposure as identical, which would be acceptable if the potency of chemicals remains constant across a lifetime. There are a number of reasons to believe that potency is not equal across life stages, including dose-response and biological plausibility. Human data on early-life exposures and carcinogenesis are limited, i.e., DES (*in utero*) and low-level radiation; the epidemiologic studies suggest associations, but do not allow comparisons of life stages. Animal data suggest a very significant difference in cancer incidence when exposure begins at postnatal day 1 for 5 weeks compared to adult exposures. In general, combined perinatal and adult exposure increases the incidence of a given type of neoplasm. The increase is fairly small and there is some indication of a reduced latency period.

EPA looked for rodent carcinogenicity studies allowing the comparison among early exposure, postnatal exposure, and standard adult exposure. Data were located on 16 chemicals, ten of which are "classic" compounds acting through a mutagenic MOA; the other six had a nonmutagenic MOA. The endpoint was an estimate of tumor incidence above the control rate per week of exposure during early-life and adult periods. Ideally, these ratios would be indicators of early life potencies, but there are uncertainties, such as dose.

In summary, for chemicals with a mutagenic mode of action, at least 72% of the studies had

ratios greater than one, Dr. Barton said. The acute and multiple exposure studies are essentially the same. When the analysis controls rigorously for dose and latency, it does not change the observation that mutagenic chemicals have greater potency in early life stages.

Pubertal periods of tissue development are an exceptional age-dependent pattern, Dr. Barton noted. Differences between the results of the analyses of the acute and the multiple exposure studies relate to the tumor sites: all but one of the multiple exposure studies were of the liver. Among the acute studies, the lung is a notable difference. In the human radiation studies, the lung was also different, and the limited human data were consistent with the animal data.

Dr. Marty suggested that the acute studies may be missing the window of susceptibility, and that the chronic exposure studies are more important for quantification. Dr. Barton said that both types of study are important: the chronic are relevant to humans, and are less likely to miss the window, but the acute studies are better regarding dose, etc. Both types provide different strengths and weaknesses that help support the overall position.

Dr. Barton said that in EPA's judgment, there was substantial evidence that cancer susceptibility is not equal across the lifespan.

Dr. Barton then presented the logic behind EPA's proposed risk assessment approach. If the data are available, the assessor should try to use the tumor data. If adult data are available, they should be used. If information on the MOA is available, and it is mutagenic, then the assessment moves to linear extrapolation and an age dependent adjustment factor should be used. If the agent is not mutagenic, the assessor should do the appropriate nonlinear analysis, depending on the strength of the database, or go to the default linear analysis.

Summarizing the approach in the SGACS for agents with a mutagenic mode of action, Dr. Barton said that the age period of concern was birth through the completion of pubertal tissue development. However, EPA did not have the data to support numerous subdivisions; the Agency could support the separation of the 0-2 year age group. As for the values of the adjustment factors, 10 was the median of the studies analyzed, and seemed to be supported by the theoretical analyses; 3 seemed consistent with the decline from juvenile to adult sensitivity. For lifetime exposure, the increase in lifetime risk is fairly modest (usually less than a factor of 2). This small increase in lifetime risk seemed reasonable and consistent with the animal studies, and was a "check" on whether the adjustment factors made sense.

In summary, Dr. Barton said that the database supports unequal cancer risks. The strongest information was available for agents with a mutagenic MOA; EPA proposed a decision tree and an approach for these chemicals. Future efforts will address *in utero* exposures and chemicals with other MOAs.

Dr. Marty commented that using the human radiation data in more than a supporting role would get around human-to-animal extrapolation and pharmacokinetic issues. Dr. Handwerger

commented that the 2-15 age group seemed counterintuitive, as a 2-year-old is very different from a 15-year-old, and suggested shortening the age range. Dr. Sweeney asked if EPA had attempted to separate out the studies with prenatal exposures; Dr. Barton said that the only studies with prenatal data were the Chhabra studies. Dr. Vetter commented that the document should emphasize the level of uncertainty in arriving at the values in the SGACS. He also asked how the SGACS might be used. Dr. Wood said that the SGACS are general guidance, to be used in risk assessments, but not in the regulatory arena.

Dr. Goldstein commented that the value for the adjustment factor was not calculated, but is a measure of central tendency, i.e., a value judgment was made. Dr. Portier noted that public commenters had raised questions about data quality and asked if EPA had set in advance any data quality standards. Dr. Barton said that EPA was aware in advance that many of the studies in the scientific literature would not comply with Good Laboratory Practices, but that it would have to rely on those studies. Dr. Portier also asked if EPA had considered data on environmental causes of cancer, e.g., hepatitis B with aflatoxin, or passive smoking. Dr. Barton said that those exposures were not considered. Dr. Marty mentioned that CalEPA has identified some 800 studies with prenatal exposures. Dr. Barton said that EPA would be pleased to include a citation to those studies.

Dr. Heeringa said that latency is perhaps the most potent age-specific effect, and it has not been separated out in EPA's model, although he is not sure that would be possible. He said that EPA's factors seem more plausible for lifetime risk assessments, than for assessments of shorter periods of time. Dr. Barton said that the approach would be used for less-than-lifetime scenarios. Dr. Portier asked if EPA had done any other analyses than those presented. Dr. Cogliano said that EPA had focused on the ratios as a pragmatic answer to the question of how to calculate risk for early life exposures.

Dr. Anderson noted that, for the nonmutagenic agents, EPA indicated that the linear model would suffice. He commented that it would be the adult MOA that would be used for modeling at low dose, however. Dr. Cogliano acknowledged that there was an implicit assumption that the MOA would be the same.

Charge Question #1

Dr. Klaunig said that overall, the analysis is accurate, reliable, and unbiased, based on the available data. Some areas need improvement, including the important issue of further definition or clarification of terms, such as mutagenesis, DNA-reactive, genotoxic, nongenotoxic, perinatal, infant, and mutagenic mode of action. He suggested that a glossary or appendix be added.

Dr. Klaunig pointed out that it is important to address whether the tumors are phenotypically and genotypically the same in adult and juvenile animals, as biological differences affect the MOA.

He said that some tables are incomplete, e.g., that tumor type should be presented; that control groups be included. He recommended that a large group of studies with data on neonatal and newborn exposures be referenced and commented on.

Regarding age groupings, Dr. Klaunig suggested that the document address the rodent ages that correlate with the human age groupings (0-2, 2-15, 15+), as this would be helpful in comparing susceptibility. Dr. Klaunig said that the document should indicate the requirements for deciding on a MOA, and should clarify that the MOA applies to adults and infants. He recommended a reference to the Cancer Guidelines to clarify whether information from one strain and one sex would be sufficient to invoke the default that the infant is more sensitive. Dr. Klaunig also recommended that a comment on the body of literature on hormesis (low-dose protective effects) be included. He suggested that the document address only agents with a mutagenic MOA, as he found the addition of the non-genotoxic MOAs to be confusing.

Dr. Marty recommended that the age groupings be reconsidered. She also said that additional studies are available and should be included. An appendix might be useful in supporting EPA's arguments. She also urged EPA to review the tables in the SGACS to correct errors.

Dr. Portier expressed a concern that the evidence that mutagenic compounds have a linear dose response, and hence a linear MOA, is not supported by the data. He urged EPA to work toward agreement between the SGACS and the Cancer Guidelines on this topic.

Dr. Luderer called for the inclusion of a qualitative assessment of other studies where juvenile exposures were examined in one study and adult exposures in another. Dr. Anderson concurred, noting that such information would be helpful, in that it would place the studies included in the document in context with the other studies available. Dr. Portier commented that it is important for users of the SGACS to know whether the literature cited presents a comprehensive review of the literature. Dr. Marty noted that the Agency must use the available data, and will add new data as they become available; she also noted that the document represented a default approach. Dr. Anderson noted that discussing additional data would strengthen EPA's arguments. Dr. Handwerger urged EPA to attempt to address the issue of additional research, noting that the available literature was old and limited in scope. Dr. Sweeney suggested that criteria for choosing studies and excluding studies would be very helpful.

Charge Question #2

Dr. Luderer said that the Agency did not do a quantitative analysis because no studies with both juvenile and adult exposures were available; however, there are a number of studies that show increased tumors with prenatal or neonatal exposure vs. adult exposure that could be cited. Dr. Luderer raised some specific points for the Agency's attention: to pursue getting the unpublished data cited in the 1995 Neubold study and to clarify the discussion of tamoxifen (p. 18). Overall, Dr. Luderer said, the weight of evidence supports an increased risk due to these chemicals, and the Agency should consider them at greater length and consider developing

guidance. Dioxins are not mentioned in the SGACS document; it would be useful to discuss them qualitatively to bolster the argument that there is increased susceptibility for some of the chemicals with nonmutagenic MOAs.

Dr. Goldstein noted some areas where there are reasons for concern. Agents with endocrine effects raise concerns in the perinatal period and adolescence; however, there are presently not enough data to generalize from them to the broader categories of nonmutagenic carcinogens. It is appropriate to reflect areas where there is greater concern, he said, but the depth to which the discussion should go is uncertain. His personal judgment is that concerns should be emphasized, and recommendations put into the areas of future research. Any agent that produces a persistent life long change in the risk of tumors, e.g., dioxins and breast cancer, will have a much more profound effect on lifetime risk assessments than anything related to a short period of exposure. There are clearly not enough data, and the panel needs to make recommendations for future research.

Dr. Marty suggested that EPA should attempt to quantify differences in susceptibility for a few of the estrogen compounds. Dr. Goldstein wondered if the SGACS was the appropriate place for such an attempt. Dr. Portier commented that the data for chemicals with a mutagenic MOA are no worse or no better than the data for chemicals with a nonmutagenic MOA for perinatal exposure; therefore, there is no reason not to do the same thing for the nonmutagenic chemicals as was already done for the mutagenic chemicals. If the data support the approach for one group, they also support the approach for the other, he said.

Dr. Anderson said that it is problematic to expect a lumped together dataset (i.e., for the nonmutagenic chemicals, to be cohesive. He recommended strengthening the language related to treating the chemicals on a case-by-case basis, and suggested treating endocrine disruptors as a class of chemicals with nonmutagenic MOAs. Dr. Portier commented that there is not a single mutagenic MOA, and that there is also a misconception that mutagenic implies linearity, and nonmutagenic may imply a nonlinear relationship. The concept that the nonmutagenic group consists of many cases is a good point, he said, but the point holds for the mutagenic group as well. Dr. Goldstein commented that mutagenic could be better defined in the document. Dr. Portier said that the Agency's default approach was a good broad spectrum approach.

Dr. Anderson asked if the panel was suggesting that the Agency use a more generic approach and apply it to all carcinogens, i.e., if there was a reason to separate the mutagenic and nonmutagenic chemicals. Dr. Portier commented that that would be in keeping with the Cancer Guidelines, namely, providing a default and the factors that would move the assessor away from it. Dr. Anderson said that this was a significant piece of advice to the Agency, and that the panel needed to justify its position that EPA develop generic guidance on mutagenic and nonmutagenic chemicals. Dr. Cogliano commented that if there are critical data gaps, the assessor would use the default; if there is sufficient confidence in the available data, and then the default is not invoked. This change in philosophy is stated in the Cancer Guidelines. The panel suggested that the Guidelines be referenced. Dr. Anderson said that overall, the panel could

recommend that the Agency move ahead on both the SGACS and the Guidelines so that they appear as a package, and could encourage cross-referencing and a glossary of definitions.

Charge Question #3

Dr. Anderson said that the committee believes that there is a differential life stage susceptibility to some chemicals and that the overall approach used in the SGACS is a good one. He said that one question for the Agency is what other means to accomplish the approach were considered. Dr. Anderson said that the committee felt that using an adjustment to the slope factor is a useful and strong approach. He noted that many of the issues related to this question had already been discussed, e.g., that the database for chemicals with a mutagenic MOA is larger and a bit stronger, so the Agency proposed a specific default, and the committee has discussed its recommendation for nonmutagenic chemicals.

At 12:00 noon, the meeting was adjourned for lunch. The meeting resumed at 1:40 p.m.

Charge Question #4

Dr. Handwerger commented that the decision to separate the age groups at 0-2 years and 2-15 years was subjective. He found the 0-2 age grouping to be reasonable in terms of growth and development, but said that there is a problem with the 2-15 age grouping, because puberty begins at age 8 in females and 9 in males. Therefore, the age 2-9 group is physiologically different than the age 9-15 group. He proposed that EPA consider age groupings of 0-2, 2-9, and 9-15 in the SGACS. He noted that an adjustment factor would need to be selected for the third age group, and that he was not clear how that would be done.

Dr. Sweeney said that she was in agreement with most of Dr. Handwerger's comments. She said that the age groups could be 0-2, 2-8, 8-11, and 11-15, but that it was possible to break them down too finely. She noted that the overlap in the sexes at puberty is close enough that it might not be worth the effort to attempt to separate by sex. Dr. Sweeney commented that the human data are sparse, but that there are some data to support the recommended revised groupings.

Dr. Goldstein wondered whether the panel should suggest that EPA consider a different adjustment for endocrine sensitive organs during the period of rapid growth. Dr. Luderer said that applying a greater factor during puberty for endocrine-active compounds would be reasonable, and Dr. Marty concurred.

Dr. Portier encouraged the Agency to broaden the language about alternatives, e.g., to look at the possibility of flexible time frames, or classes of default times depending on the type of tumor involved. He also commented that the 2-9 age grouping should be seriously considered.

Committee members discussed keeping 3 as the value for the adjustment factor. Dr. Handwerger suggested that the factor be greater than 3 for endocrine disruptors in the 9-15 age groups.

Charge Question #5

Dr. Vetter cautioned that a precise estimate of cancer risk for all age groups might be misleading without serious discussion of the uncertainties, variance, etc. Radiation is a strong carcinogen at high doses, and a weak carcinogen at low doses, he said, and the original authors forced the data into a linear model, ignoring this fact. The SGACS document needs to clearly state that the values chosen are a policy decision and clearly state how they will be used.

Dr. Heeringa addressed the appropriateness of the adjustment factors in the context of the model used. It would clearly be good to have a model that covers many factors fully, including covariates, he said, but the data are not available to make such models. The data used to develop the adjustment factors are integrated over a lifetime, and the model does not allow for potential latency of effects. The longer the time period for which the model is used, the more realistic the applicability of the data will be to the actual risk. Statistically, it is not clear that the 10X adjustment factor for the 0-2 age group is the appropriate factor, Dr. Heeringa said, although it is a plausible best estimate based on the available data. A bigger issue is whether the values are really health-protective.

Dr. Portier commented that the context in which the data are collected affects the interpretation of the analysis. Representative data are the ultimate scientific goal, because the analysis would then apply to the general population of outcomes. Comprehensive data are more difficult to interpret, but of value. Selected data give some guidance and anecdotal data only a very crude estimate of the range of outcomes. Dr. Portier said that the toxicological data used in developing the adjustment factors are between anecdotal and selective; the data may support EPA's position, but they have not been scientifically challenged. He offered several suggestions for additional statistical analysis. Dr. Portier also called for discussion of how the analysis represented the central tendency or range.

Charge Question #6

Dr. Marty suggested that EPA should look at estrogen agonists and antagonists and related hormonal mechanisms next, and noted that the analysis would be constrained by the available data. Dr. Portier commented that it might be worth waiting for two comprehensive NTP studies, which will come out in the next two years. Dr. Anderson said that the panel could make that recommendation. Dr. Portier suggested evaluation of gene-environment interactions, which could provide guidance for specific classes of compounds. Dr. Anderson said that time-to-tumor needs to be incorporated; it would enlighten the understanding of latency, etc. Dr. Luderer suggested that EPA consider agents that have been shown to produce, with exposure in the perinatal period, permanent changes in susceptibility to other carcinogens through life.

Charge Question #7

Dr. Luderer said that a similar analysis could be done for animal studies in which the mother was dosed during different periods of gestation. Dr. Goldstein said that it was unclear if transplacental studies would give data applicable to human risk, and suggested that doing pharmacokinetic research to better understand the slope factor might be helpful. Dr. Marty noted that some studies used by EPA may have missed the window of susceptibility, and that EPA needs to look at all the studies. Dr. Anderson said that the question is whether to integrate the data qualitatively or quantitatively, which is much more difficult.

Charge Question #8

Dr. Handwerger noted the need for critical and basic fundamental data, and suggested that the Panel recommend additional partnering with other agencies on research to address these critical needs. Dr. Marty suggested recommending that EPA work with NTP and others to prioritize the research, based on what is known about the extent of exposures in the U.S. population. Dr. Goldstein proposed that experimental designs that address deficiencies, e.g., time to tumor, are needed, although the studies will be large and expensive. Dr. Marty suggested that the panel recommend that studies be included in the National Children's Study. Dr. Anderson commented that methodological issues need to be addressed, e.g., how can chronic animal studies be modified to tease out these questions, since current designs and methodologies were not developed to answer them. Dr. Portier suggested that the Panel make it clear that the Agency will have to consider overall priorities, and clearly provide alternative approaches to acquiring information.

Executive Summary

Dr. Anderson asked the Panel to consider the following points for inclusion in the Executive Summary at this time, instead of during Wednesday's session, as originally scheduled:

1. There is a wealth of other data that support the conclusion of differential susceptibility, and EPA should include additional references to support its conclusion.

2. Both the Cancer Guidelines and the SGACS need to stay together; the Agency should move forward with finalizing them.

3. The science on both the mutagenic and nonmutagenic chemicals seems to be supportive of differential susceptibility. The Panel felt it was difficult to differentiate the two groups, and that, in a broad sense, they needed to be dealt with together.

4. The Panel felt that the science supported differences in risk at puberty, and recommended three age groups, even though the adjustment factor might be the same.

5. For future action, the Panel recommended that the next MOA to be addressed would be

endocrine disruptors, including issues of estrogenicity and antiestrogenicity.

In discussion, the Committee suggested including statements supportive of EPA's general approach and appreciative of the hard work put in to developing the document. Dr. Anderson asked all members to think about and provide additional points for the Executive Summary.

Dr. Anderson thanked the Panel members for their work. The meeting adjourned at 3:45 p.m.

Wednesday, May 14, 2003

The Panel discussed and revised its draft responses to the Charge Questions. Time was spent on selecting the points to be highlighted in the Executive Summary and in the letter to the Administrator. These key recommendations were the focus of the discussion and were extensively revised. A teleconference to review the draft report was discussed and a mid-June timeframe was established.

The meeting adjourned at approximately 4:00 p.m.

Respectfully Submitted:

/Signed/

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Dr. Suhair Shallal
Designated Federal Official

Certified as True:

/Signed/

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Dr. Henry Anderson, Chair
Supplemental Guidance for Assessing Cancer Susceptibility (SGACS) Review Panel

ATTACHMENTS

Attachment A	Roster of SGACS Review Panel Members http://www.epa.gov/sab/pdf/sgacsrproster.pdf
Attachment B	Sign-in Sheets, available
Attachment C	Meeting Agenda http://www.epa.gov/sab/03agendas/sgacsrp051203a.pdf
Attachment D	Slides, Dr. Bill Wood, "Science Advisory Board Review of EPA's Draft Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens," available
Attachment E	Charge Questions, attached
Attachment F	Slides, Dr. Jim Cogliano, "Cancer Risk Assessment and Children," available
Attachment G	Slides, Dr. Hugh Barton, "Draft Children's Supplemental Cancer Guidance," available

ATTACHMENT E

CONCERNING THE SUPPLEMENTAL GUIDANCE FOR ASSESSING
CANCER SUSCEPTIBILITY FROM EARLY-LIFE EXPOSURE TO CARCINOGENS

The Agency seeks the Science Advisory Board's review of the soundness of the Agency's position that the Agency's analysis and the underlying scientific information support the conclusion that there is greater susceptibility for the development of tumors as a result of exposures in early lifestages as compared with adults to chemicals acting through a mutagenic mode of action.

1. Please comment on whether the Agency's analysis as applied to chemicals acting through a mutagenic mode of action is accurate, reliable, unbiased and reproducible. Likewise, please comment on whether the underlying scientific information used to develop the guidance is accurate, reliable, unbiased and reproducible. Are there any key studies that the Agency has overlooked in reaching this conclusion?

2. For chemicals acting through non-mutagenic modes of action, the Agency concludes that a range of approaches needs to be developed over time for addressing cancer risks from childhood exposures. Please comment on the Agency's conclusion that the scientific knowledge and data are insufficient at this time to develop generic guidance on how to address these chemicals and that a case-by-case approach is more suitable. Is the SAB aware of any additional data for chemicals acting through non-mutagenic modes of action relevant to possible early lifestage sensitivity?

3. Assuming that it is appropriate to conclude that there is differential lifestage susceptibility to chemicals acting through a mutagenic mode of action, the Agency's guidance uses a default approach that adjusts cancer slope factors (typically from conventional animal bioassays and/or epidemiologic studies of adult exposure) to address the impact of early lifestage exposure. Please comment on whether the approach is justified by the available data? Can the SAB suggest other approaches that might be equal or more appropriate?

4. When considering differential susceptibility, the Agency's guidance separates the potential susceptible period into two age groups, 0 - 2 years and 2 - 15 years. These groupings were based on biological considerations rather than exposure considerations. The first grouping, 0 - 2 years of age, is meant to encompass a period of rapid development and the second grouping, 2 – 15 years of age, was selected to extend through middle adolescence approximately following the period of rapid developmental changes during puberty. Please comment on the scientific rationale that was used to justify these age groupings. Can the SAB suggest other plausible ways to make these groupings?

5. The guidance provides a quantitative approach to account for the greater susceptibility of

early-life exposure to chemicals that act through a mutagenic mode of action. An adjustment factor of 10 is applied to the cancer slope factor (derived from animal or epidemiology studies) for exposures before 2 years of age, a factor of 3 is applied for ages between 2 and 15 years, and no adjustment is applied after the age of 15. Please comment on whether the data and EPA analysis are scientifically sufficient to support these adjustment factors. Are sufficient data, including breadth of chemicals, available to make these determinations?

OTHER QUESTIONS

6. The Agency recognizes that consideration of children's risk is a rapidly developing area and, therefore, the Agency intends to issue future guidance that will further refine the present draft guidance and possibly address other modes of action as data become available. The Agency welcomes the SAB's recommendations on other modes of action that may be most fruitful to assess in similar future analyses.

7. The analysis presented in the current Guidance relies on postnatal studies. Can the SAB recommend how to best incorporate data from transplacental or *in utero* exposure studies into future analyses?

8. The Agency welcomes the SAB's recommendations on critical data needs that will facilitate the development of future guidance addressing differential lifestage susceptibility.